Economics of Antibiotic Resistance

Ramanan Laxminarayan

Latsis Symposium, 2015
I. Increasing incomes and access to antibiotics are saving lives but are not a good substitute for public health
Bacterial diseases are still major killers in developing countries because of lack of access to antibiotics

O’Brien et al, Lancet 2009
What are we asking of antibiotics?

**Figure 1.1**

Crude infectious disease mortality rate in the United States, 1900–1996

- **Influenza pandemic**
- **40 states have health departments**
- **Last human-to-human transmission of the plague**
- **First continuous municipal use of chlorine in water in United States**
- **First use of penicillin**
- **Salk vaccine introduced**
- **Passage of Vaccination Assistance Act**

**Source:** Adapted from Armstrong, Conn et al. (1999).
Substitute for immunization, infection control and water/

Crude infectious disease mortality rate in the United States, 1900–1996

- Influenza pandemic
- South Asia
- First use of penicillin
- Salk vaccine introduced
- Passage of Vaccination Assistance Act
- Last human-to-human transmission of the plague
- First continuous municipal use of chlorine in water in United States
- 40 states have health departments

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Source: Adapted from Armstrong, Conn et al. (1999).
Vaccines can be effective
Invasive disease caused by Pneumococci in children under two declined in the US post pneumo vaccination

Effect of PCV7 introduction on antibiotic prescriptions and ambulatory care visits

Zhou et al, Pediatrics 2008
Effect of PCV7 introduction on antibiotic prescriptions and ambulatory care visits

Antibiotic prescriptions attributable to acute otitis media decreased from 1244 to 722 prescriptions per 1000 person-years – a 41.9% reduction.

Zhou et al, Pediatrics 2008
Antibiotic consumption is increasing in developing countries...

Per capita total antibiotic use, retail sector, 2005-2010

Source: Based on data obtained under license from IMS Health MIDAS™ (January 2005-December 2010); IMS Health Incorporated. All Rights Reserved.
Extended-spectrum macrolide use is highly prevalent in the United States, and increasing in developing countries.

Data source: Based on data obtained under license from IMS Health MIDAS™ (January 2005-December 2010); IMS Health Incorporated. All rights reserved.
Last-resort drugs are widely sold on the retail market.

Per capita total carbapenem use, retail sector, 2005-2010

Source: Based on data obtained under license from IMS Health MIDAS™ (January 2005-December 2010); IMS Health Incorporated. All Rights Reserved.
Hospital use of carbapenems is rapidly growing

Source: Based on data obtained under license from IMS Health MIDAS™ (January 1999-December 2010); IMS Health Incorporated. All Rights Reserved.
Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data

Thomas P Van Boeckel, Sumanth Gandra, Ashvin Ashok, Quentin Caudron, Bryan T Grenfell, Simon A Levin, Ramanan Laxminarayan

Summary

Background Antibiotic drug consumption is a major driver of antibiotic resistance. Variations in antibiotic resistance across countries are attributable, in part, to different volumes and patterns for antibiotic consumption. We aimed to assess variations in consumption to assist monitoring of the rise of resistance and development of rational-use policies and to provide a baseline for future assessment.

Lancet Infect Dis 2014
Published Online
July 10, 2014
http://dx.doi.org/10.1016/S1473-3099(14)70780-7
Figure 2: Consumption of antibiotics in 2010

Figure: Compound annual growth rate (CAGR) of total antibiotic consumption in Standard Units (SU) per capita for the period 2000-2010 across select countries.
Van Boeckel et al, Lancet Inf Dis, 2014
Antibiotic sales data can predict influenza in the United States

**Figure 1.** Observed and fitted antibiotics series from 2000 to 2007. The solid line represents the actually observed antibiotics series; the dashed line represents the fitted antibiotics series from the time series regression model that uses influenza-like illness as an explanatory series.
Carbapenem-resistant Acinetobacter baumannii

Year: 1999

Percentage resistant:
- < 10%
- 10 - 20%
- 20 - 40%
- 40 - 60%
- > 60%
- Inadequate data

National rate:
Mortality outcomes are worse in neonates with resistant infections.

NEW YORK OFFICER FACING NO CHARGES IN CHOKEHOLD CASE

Grand Jury’s Decision in Fatal Encounter Draws Protests — U.S. to Investigate

By J. DAVID GOODMAN and AL BAKER

A Staten Island grand jury on Wednesday ended the criminal case against a white New York police officer whose chokehold on an unarmed black man led to the man’s death, a decision that drew condemnation from elected officials and touched off a wave of protests.

The fatal encounter in July was captured on video and seen around the world. But after watching the footage and hearing from witnesses, including the officer who used the chokehold, the jury deliberated for less than a day before deciding that there was not enough evidence to go forward with charges against the officer, Daniel Pantaleo, 28, in the death of the man, Eric Garner, 43.

Officer Pantaleo, who has been on the force for eight years, appeared before the grand jury on Nov. 21, testifying that he did not intend to choke Mr. Garner, who was being arrested for allegedly selling loose cigarettes. He described the maneuver as a take-down move, adding that he never thought Mr. Garner was in mortal danger. [Page A28]

The decision came barely a week after a grand jury found no criminality in the actions of another white police officer, Darren Wilson, who shot and killed Michael Brown, an unarmed 18-year-old black man in Ferguson, Mo.

After the news from Staten Island, a wave of elected officials renewed calls for Justice Department intervention, saying the grand jury’s finding proved that justice could be found only in the federal courts. By the evening, the department announced it would open a civil rights inquiry.

On the streets of the city, from Tompkinsville to Times Square, many expressed their outrage with some of the last words Mr. Garner uttered before being wrestled to the ground: “This can’t breathe,” others shouted.

While hundreds of angry but generally peaceful demonstrations took to the streets in Manhattan as well as in Washington and other cities, the police in New York reported relatively few arrests, a stark contrast to the riots that unfolded in Ferguson in the hours after the grand jury decision was announced.

Continued on Page A29

U.S. and Iran Both Attack ISIS, But Try Not to Look Like Allies

By TIM ARANGO and THOMAS ERDBRINK

BAGHDAD — Iranian fighter jets struck extremist targets in Iraq recently, Iranian and American officials have confirmed, in the latest display of Tehran’s new willingness to conduct military operations openly on foreign battlefields rather than covertly and through proxies.

The shift stems in part from Iran’s deepening military role in Iraq in the war against the Sunni extremists of the Islamic State. But it also reflects a profound gets in a buffer zone that extends 25 miles into Iraq.

The new military approach highlights an unusual confluence of interests in both Iraq and Syria, where Tehran and Washington find themselves fighting the same enemy in an increasingly public fashion. While there is no direct coordination between Iran and the United States, there is a de facto nonaggression pact that neither side is eager to acknowledge.

‘Superbugs’ Kill India’s Babies And Pose an Overseas Threat

By GARDINER HARRIS

AMRAVATI, India — A deadly epidemic that could have global implications is quietly sweeping India, and among its many victims is tens of thousands of newborns dying because once miraculous care no longer works.

These infants are born with bacterial infections that are resistant to most known antibiotics, and more than 80,000 die last year as a result, a recent study found. While that is still a fraction of the nearly 800,000 newborns world, and this will require treating an increasing number of neonates who have sepsis and pneumonia,” said Dr. Vineet Paul, chief of pediatrics at the All India Institute of Medical Sciences and the leader of the study. “But if resistant infections keep growing, that progress could slow, stop or even reverse itself. And then would be a disaster for not only India but the entire world.”

In visits to neonatal intensive care wards in five Indian states,
II. Drivers of antibiotic use relate to incentives and behavior of patients, physicians, pharma, payers and healthcare institutions.
Incentives for Physicians

• Satisfying patient expectations
### TABLE 5

**Frequency of Antibiotic Prescribing by Factors Related to Patients’ Expectations of Antibiotics (N = 482)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. (*) (%)</th>
<th>Antibiotic Prescribed No. (%</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient expects antibiotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>290 (60)</td>
<td>213 (73)</td>
<td>2.6 (1.7-3.9)</td>
</tr>
<tr>
<td>No</td>
<td>150 (31)</td>
<td>78 (52)</td>
<td>reference</td>
</tr>
<tr>
<td>No answer</td>
<td>42 (9)</td>
<td>28 (67)</td>
<td></td>
</tr>
<tr>
<td>Clinician believes patient expects an antibiotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>298 (62)</td>
<td>236 (79)</td>
<td>4.7 (3.2-7.1)</td>
</tr>
<tr>
<td>No</td>
<td>182 (38)</td>
<td>81 (45)</td>
<td>reference</td>
</tr>
<tr>
<td>No answer</td>
<td>2 (&lt;1)</td>
<td>2 (100)</td>
<td></td>
</tr>
<tr>
<td>Antibiotic helped similar illness in the past</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>284 (59)</td>
<td>212 (75)</td>
<td>4.5 (2.9-6.9)</td>
</tr>
<tr>
<td>No</td>
<td>170 (35)</td>
<td>88 (52)</td>
<td>reference</td>
</tr>
<tr>
<td>Don’t know</td>
<td>19 (4)</td>
<td>12 (63)</td>
<td></td>
</tr>
<tr>
<td>No answer</td>
<td>9 (2)</td>
<td>5 (56)</td>
<td></td>
</tr>
</tbody>
</table>

*NOTE: Because some questions were unanswered, the numbers may not add up to 482.

*In outpatients with nonspecific upper respiratory infections, acute bronchitis, or acute sinusitis.

OR denotes odds ratio; CI, confidence interval.
Health insurance increases prescribing

Table 4. Use of oral, injected, and all antibiotics per person per year by level of family income and insurance plan

<table>
<thead>
<tr>
<th>Antibiotic use and income tertile*</th>
<th>Free plan (N = 1935)</th>
<th>Cost-sharing plans (N = 3830)</th>
<th>Ratio of free to cost-sharing (95% confidence interval)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of antibiotics</td>
<td>Number per person</td>
<td>Number of antibiotics</td>
</tr>
<tr>
<td>Oral antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper one-third</td>
<td>548</td>
<td>0.94</td>
<td>723</td>
</tr>
<tr>
<td>Middle one-third</td>
<td>577</td>
<td>0.93</td>
<td>669</td>
</tr>
<tr>
<td>Lower one-third</td>
<td>442</td>
<td>0.72</td>
<td>386</td>
</tr>
<tr>
<td>All incomes</td>
<td>1670</td>
<td>0.85</td>
<td>1825</td>
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<td>Injected antibiotics</td>
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<td>75</td>
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<td>45</td>
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<td>221</td>
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<td>Upper one-third</td>
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<td>1.02</td>
<td>812</td>
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<td>1.04</td>
<td>744</td>
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<td>480</td>
<td>0.78</td>
<td>431</td>
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<td>1857</td>
<td>0.96</td>
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*Numbers shown for income tertiles do not sum to totals because income was unknown for 138 claims on the free plan and 59 on the cost-sharing plans.
†Taylor's series 95% confidence intervals [12]; ratio and confidence intervals calculated using 8 significant digits.
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What happens when antibiotics are provided free?

Table 2: Average Percentage Change in prescriptions 1 year into the program

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Note: The changes before the program are calculated using data from November 2005 to October 2006, and the changes after the program are based on data from November 2006 to October 2007.

Overall increase in antibiotic prescriptions as well as substitutions to covered antibiotics from not-covered antibiotics.

Li and Laxminarayan, Health Economics, 2013
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Li and Laxminarayan, *Health Economics*, 2013
Hospital Incentives

- Antibiotics may be a substitute for infection control
- Infection control is often not compensated but longer hospital stays are beneficial to the hospital
III. In the livestock sector, the tremendous increase in demand for animal protein will drive continued use of antibiotics in sub-therapeutic concentrations without changes in regulatory policy
Increase in demand for poultry in India and China between 2000 and 2030

FAO, 2011
Amounts, in mg, of veterinary antibacterial agents sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced plus estimated live weight of dairy cattle. *2005 data. **The substances included vary from country to country.

Global trends in antimicrobial use in food animals

Thomas P. Van Boeckel\textsuperscript{a,1}, Charles Brower\textsuperscript{b}, Marius Gilbert\textsuperscript{c,d}, Bryan T. Grenfell\textsuperscript{a,e,f}, Simon A. Levin\textsuperscript{a,g,h,1}, Timothy P. Robinson\textsuperscript{j}, Aude Teillant\textsuperscript{a,e}, and Ramanan Laxminarayan\textsuperscript{b,e,i,1}

\textsuperscript{a}Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08544; \textsuperscript{b}Center for Disease Dynamics, Economics & Policy, Washington, DC 20036; \textsuperscript{c}Université Libre de Bruxelles, B1050 Brussels, Belgium; \textsuperscript{d}Fonds National de la Recherche Scientifique, B1000 Brussels, Belgium; \textsuperscript{e}Princeton Environmental Institute, Princeton, NJ 08544; \textsuperscript{f}Fogarty International Center, National Institutes of Health, Bethesda, MD 20892; \textsuperscript{g}Beijer Institute of Ecological Economics, 10405 Stockholm, Sweden; \textsuperscript{h}Resources for the Future, Washington, DC 20036; \textsuperscript{i}International Livestock Research Institute, 00100 Nairobi, Kenya; and \textsuperscript{j}Public Health Foundation of India. New Delhi 110070, India
Global antimicrobial consumption in livestock (top) and average standard deviation of estimates (bottom)

van Boeckel et al, *PNAS*, 2015
Largest consumers of antimicrobials in livestock in 2010 and 2030

A) Largest five consumers of antimicrobials in livestock in 2010
B) Largest five consumers of antimicrobials in livestock in 2030 (projected).
C) Largest Increase in antimicrobial consumption between 2010 and 2030,
D) Largest relative increase in Antimicrobial consumption between 2010 and 2030.

van Boeckel et al, *PNAS*, 2015
• Global average annual consumption of antimicrobials per kilogram of animal produced was 172 mgs per kg for cattle, chicken and pigs

• Global consumption of antimicrobials in food animal production was estimated at 63,151 (±1,560) tonnes in 2010 and is projected to rise by 67%, to 105,596 (±3,605) tonnes by 2030,
  ‣ In hotspots like India where areas of high consumption (30 kg per km2) for industrial poultry production are expected to grow 312% by 2030

(van Boeckel et al, PNAS, 2015).
Improvement in the Average Daily Growth (ADG) of pigs fed antibiotics over time

- Zimmerman, 1986
- Hays, 1978
- Hays, 1978
- Hays, 1978
- Miller, 2005
- Van Lunen, 2003
- Dritz, 2002
- Dritz, 2002
- Miller, 2003
Difference in average daily growth between animals raised with and without AGPs

- **1980s literature**
- **2000s literature**

% difference

- **Cattle**
- **Chickens**
- **Pigs**

Laxminarayan et al OECD Report, 2014
Response by livestock to supplementation with growth promoters

Barug et al., 2006
Productivity reductions and costs per produced pig incurred by removing AGPs

- Increased workload (30 sec./pig at $25/hour): $0.21
- Increased medication (25500 kg valued at $9.09 million for 23.5 million pigs): $0.39
- Excess feeding days (1.6 days * $0.19/day): $0.30
- Excess mortality (0.6% * $73/pig (20kg)): $0.44

Total cost = $1.34

Source: Laxminarayan et al OECD Report, 2014
Effect of Danish ban on AGPs
Categories of regulatory framework for the use of antimicrobial for growth promotion
Potential loss in annual meat production following AGP withdrawal (in %)

Laxminarayan et al OECD Report, 2014
Potential loss in the value of annual meat production following AGP withdrawal

Laxminarayan et al. OECD Report, 2014
IV. Who will pay the price of rising resistance – implications of AMR.
Loss of first line drugs increases drug costs

Annual health gain (QALYs) in the US from procedures requiring antibiotic prophylaxis

Figure: Trends in the estimated total gains in quality-adjusted life years due to organ transplants, hip and knee replacements and open heart surgeries performed annually in the US during 1994-2013.

Data source: Data on organ transplants is obtained from the online database published by the Organ Procurement and Transplantation Network. Annual reports on National Hospital Discharge Survey are used to calculate estimates for open heart surgeries and hip and knee replacements. Estimates on total quality adjusted life years (QALYs) are calculated by multiplying QALYs per procedure obtained from studies in the US and Europe.

*For organ transplants, QALYs due to simultaneous heart and lung transplants are not included, and QALY per procedure for pancreas after kidney transplantation is used as the QALY per procedure for pancreas transplantation.

**For open heart surgeries, QALYs are only from coronary artery bypass graft (CABG).
V. Solving the problem – what can economics bring to the table?
Make better use of existing antibiotics
Find new antibiotics
Is the rate of new drug development declining?

FIGURE 1: The FDA Reboot of Antibiotic Development
Antimicrobial agents approved by FDA. The number of new antibacterial agents is shown from 1983 to 2012. (Courtesy of The American Society for Microbiology)
Trends in development of new antibiotics
Fig. 3. Antibiotic pipeline for the past 20 years.

Consider this

• Of the 61 new antibiotics approved between 1980 and 2009, 26 (43%) were withdrawn either because of toxicity or lack of market, compared with a 13% withdrawal rate for other therapeutic categories (Outterson et al 2013)

• Under the Generating Antibiotic Incentives Now (GAIN) Act in the United States new antibiotics are given 5 years of additional market exclusivity for designated Qualified Infectious Disease Products
Market Launch: 1941
Price in USD

$ 40,000

$ 20,000

$ 200

$ 100

$ 10

$ 0.10

$ 0.01

$ 0

Penicillin $ 0.1

Linezolid $ 155

Market Launch: 1941 2000

CDDEP THE CENTER FOR DISEASE DYNAMICS, ECONOMICS & POLICY WASHINGTON DC • NEW DELHI
Price in USD

$ 40,000
$ 20,000
$ 100
$ 20
$ 0.20
$ 0.10
$ 0.05
$ 0

<table>
<thead>
<tr>
<th>Drug</th>
<th>Price (USD)</th>
<th>Market Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>$0.1</td>
<td>1941</td>
</tr>
<tr>
<td>Linezolid</td>
<td>$155</td>
<td>2000</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>$181</td>
<td>2006</td>
</tr>
</tbody>
</table>
Price in USD

- Penicillin: $0.1 (Market Launch: 1941)
- Linezolid: $155 (Market Launch: 2000)
- Daptomycin: $181 (Market Launch: 2006)
- Sipuleucel-T: $31,000 (Market Launch: 2010)
Important questions

• Do we need public subsidies for new antibiotic development or will the market respond on its own?
• What is the impact of public subsidies for new drug development on stewardship?
• How can we change the rules of the game to incentivize appropriate use of new (and existing) antibiotics?
• How do we balance access with concerns about resistance?
Once an antibiotic is introduced, resistance is not far behind…

What kind of innovation?

- Combination therapies that target both essential functions and resistance factors
  - Eg. amoxicillin-clavulanate
- Repurpose old drugs to optimize dosing levels and the duration, and route of administration
  - E.g. optimized dosing of colistin to reduce toxicity and improve efficacy
- Prevent resistance by protecting non-target bacterial flora during treatments
- Point-of-care diagnostics
  - to identify both the cause of an infection and its sensitivity to common antibiotics
Q: What should we be willing to pay for a stewardship program that would enable a 1-year delay in the need for a $1 billion investment in a new antibiotic?

A: Roughly $60 million, at a modest 6% discount rate
Q: What does the US Government allocate for antimicrobial stewardship programs?

A: Zero
Q: What does the Indian Government allocate for antimicrobial stewardship programs?

A: What is a stewardship program?
Closing thoughts
Thank you